[4+2]-Cyclodimer of sabinone: formation, crystal structure, and NMR spectra

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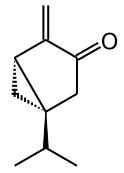
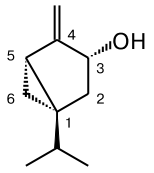
Oxidation of (+)-sabinol, (1*S*,3*R*,5*S*)-1-isopropyl-4-methylidenebicyclo[3.1.0]hexan-3-ol, by active MnO_2 afforded not the expected sabinone but only its [4+2]-cyclodimer. The molecular structure of the latter was established by X-ray diffraction analysis. The ^1H and ^{13}C NMR spectra of this cyclodimer were interpreted using 2D NMR spectroscopy.

Key words: (+)-sabinol, (1*S*,3*R*,5*S*)-1-isopropyl-4-methylidenebicyclo[3.1.0]hexan-3-ol; oxidation; sabinone; *in situ* [4+2]-cyclodimerization; X-ray diffraction analysis; 2D NMR spectroscopy.

As part of continuing studies of chemical transformations of monoterpene α-enones,[1,2] we attempted to prepare previously unknown sabinone (**1**) by oxidation of (+)-sabinol (**2**)[3—5] by active manganese dioxide[6] in light petroleum. However, we found that this reaction rapidly afforded the only product, which is a cyclodimer of the expected ketone **1**, in quantitative yield. The molecular structure of this dimer described by formula **3** was established by X-ray diffraction analysis* (Fig. 1).



1



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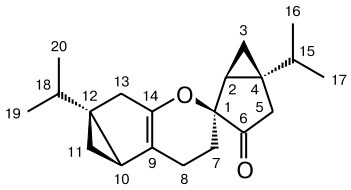
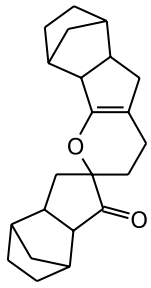


3



4

The bond lengths and bond angles in molecule **3** are close to the corresponding standard values[7] and are equal (to within 3σ) to the corresponding values in compound **4**,[8] which is the closest analog of compound **3** available in the Cambridge Structural Database (2001).[9] The only exception is the C(1)—C(6) bond, which is elongated in molecule **3** to 1.537(4) Å compared to the average value (1.514(16) Å) for the $O{=}C_{sp^2}{-}C_{sp^3}$ fragment (averaged over 312 structures).[7] Of note also is the usual shortening of the bonds adjacent to the cyclopropane fragments in molecule **3** compared to the analogous bonds in the five-membered rings of molecule **4**. The six-membered ring of molecule **3** adopts a half-chair conformation with the C(1) and C(7) atoms deviating from the plane passing through the remaining four atoms (average deviation from the plane is 0.002 Å) in opposite directions by 0.386(6) and −0.280(5) Å, respectively. The cyclopentene fragment of molecule **3** is planar (average deviation from the plane is 0.017 Å). The cyclopentane ring has an envelope conformation with the C(6) atom deviating from the plane of the remaining four atoms (average deviation from the plane is 0.011 Å) by −0.350(5) Å. It should be noted that the conformations of the rings in molecule **3** are identical with those in compound **4** with the only difference that the spiro atom in molecule **4** deviates from the plane through the remaining atoms of the cyclopentane fragment.

* The atomic numbering scheme for molecule **3** relates to the X-ray diffraction data and interpretation of the NMR spectra.

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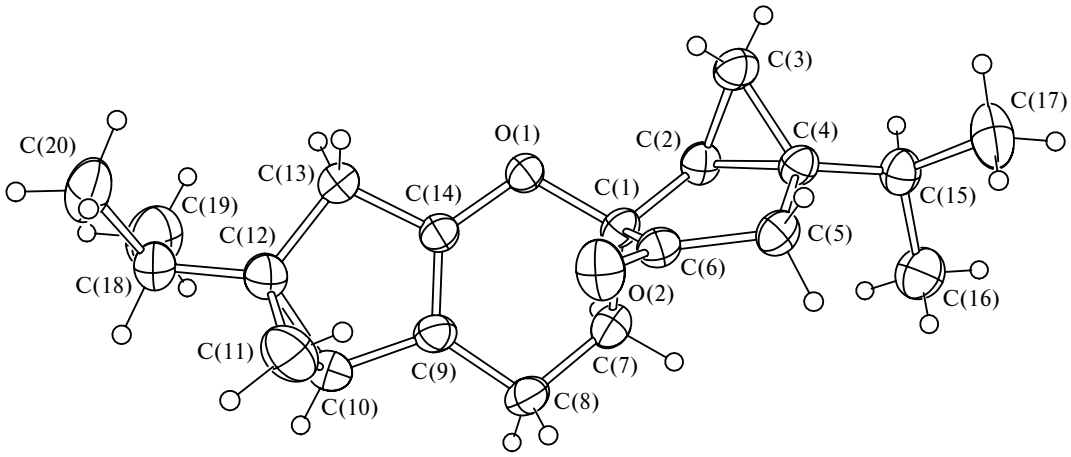

Fig. 1. Overall view of molecule **3**.

The signals in the ^1H and ^{13}C NMR spectra overlap only slightly, which allowed us to make their assignment (see the Experimental section) with the use of the data from 2D $^1H—^1H$ (COSY) and $^{13}C—^1H$ (COSY, COLOC) NMR spectroscopy. The key to the interpretation of the signals in the ^1H NMR spectrum of ketone **3** is the identification of the components of two AB systems formed by pairs of the H(5) and H(13) protons based on the large coupling constants $J_{A,B}$. Since the components of the lower-field pair of the signals is additionally split due to long-range spin-spin (homoallylic) coupling, they can be assigned to the $H(13)_A$ and $H(13)_B$ protons, respectively. In the second pair of the signals ($H(5)_A$ and $H(5)_B$), as expected, only one signal ($H(5)_B$) is split due to long-range spin-spin coupling of this proton with $H(3)_A$.

Analogous dimerization has been described earlier for cyclic α-enones containing vicinal oxo and *exo*-methylidene groups.[8,10—12] This dimerization proceeds both regio- and stereospecifically as the Diels—Alder cycloaddition. The ability of such α-enones to undergo dimerization varies substantially with their structures. On the one hand, the starting "monomers" in our investigation and in earlier studies,[8,10] cannot apparently exist and were not detected. On the other hand, pinocarvone ((1*S*,5*S*)-6,6-dimethyl-2-methylidenebicyclo[3.1.1]heptan-3-one) is quite stable, and its cyclodimer was obtained in 10% yield from the reaction mixture by oxidation of β-pinene with selenium dioxide.[11] A diterpene α-enone, which belongs to the same type but has the taxane carbon skeleton, is rather stable but undergoes gradual dimerization in a benzene solution even at ~20 °C.[12]

As early as 1951, it was found[13] that oxidation of sabinol by SeO_2 in EtOH afforded a crystalline compound with composition $C_{20}H_{28}O_2$ in 20% yield. Attempts to obtain data on its chemical structure have failed.[14] However, it can be suggested that the authors of the cited study prepared dimer **3**.

Experimental

The melting point was determined on a Boetius instrument. The IR spectrum was recorded on a Vector 22 instrument. The ^1H and ^{13}C NMR spectra were measured on a Bruker DRX-500 spectrometer (500.13 MHz for ^1H and 125.76 MHz for ^{13}C) in C_6D_6 with the use of the standard Bruker software for recording 2D COSY and COLOC spectra (9 Hz). The high-resolution mass spectrum (EI, 70 eV) was obtained on a Finnigan MAT 8200 instrument. The optical rotation was measured on a Polamat A polarimeter (at 580 nm). The TLC analysis was carried out on Silufol plates; spots were visualized by spraying with a 1% vanilline solution in H_2SO_4.

The starting (+)-sabinol with $[\alpha]_{580}^{21} = +10$ (*c* 2.33, $CHCl_3$) (*cf.* lit. data[4]: $[\alpha]_D^{21} = +8.3$ ($CHCl_3$)) was isolated from the essential oil of *Juniperus sabina* L.[4,5,15] Its ^1H and ^{13}C NMR spectra are identical with those published.[16,17]

(1´*S*,2*S*,5´*S*,5*S*,7*S*)-5´,7-Diisopropyl-3,4,5,6,7,8-hexahydro-5,7-cyclospiro(2*H*-benzopyran-2,2´-bicyclo[3.1.0]hexan)-3´-one (3). Activated MnO_2 (3.2 g, 36 mmol) prepared according to a known procedure[6] was added portionwise to a stirred solution of alcohol **2** (0.70 g, 4.5 mmol) in light petroleum (25 mL) at ~20 °C for 15 min. Then the reaction mixture was stirred for 15 min, washed with water (15 mL), and dried with anhydrous Na_2SO_4. After removal of the solvent, the residue was recrystallized from a light petroleum—AcOEt mixture to obtain product **3** as colorless crystals in a yield of 0.62 g (92%), m.p. 138—140 °C, $[\alpha]_{580}^{21}$ +31.2 (*c* 1.41, acetone). IR (CCl_4), ν/cm^{-1}: 3059, 2959, 2928, 2874, 2874, 1757 (C=O), 1683, 1300, 1247, 1179, 1055. MS, *m/z* (I_{rel} (%)): 300 $[M]^+$ (13), 257 (21), 163 (42), 151 (17), 150 (23), 149 (21), 135 (17), 121 (100), 107 (40), 91 (15). High-resolution MS, found: *m/z* 300.20762 $[M]^+$. $C_{20}H_{28}O_2$. Calculated: M = 300.20892. ^1H NMR, δ: 0.44 (ddd, $H(3)_A$, J = 8.0 Hz, J = 6.0 Hz, J = 2.5 Hz); 0.55 (dd, $H(3)_B$, J = 6.0 Hz, J = 4.0 Hz); 0.56 (t, $H(11)_A$, J = 3.5 Hz); 0.68 (d, $C(16)H_3$, J = 7.0 Hz); 0.70 (d, $C(17)H_3$, J = 7.0 Hz); 0.71 (dd, $H(11)_B$, J = 6.5 Hz, J = 3.5 Hz); 0.86 (d, $C(19)H_3$, J = 7.0 Hz); 0.93 (sept, H(15), J = 7.0 Hz); 0.94 (d, $C(20)H_3$, J = 7.0 Hz); 1.18 (dd, H(2), J = 4.0 Hz, J = 8.0 Hz); 1.29 (sept, H(18), J = 7.0 Hz); 1.37 (dt, H(10), J = 6.5 Hz, J = 3.5 Hz); 1.63 (dt, $H(6)_A$, J = 14.0 Hz, J = 5.0 Hz); 1.74 (ddd, $H(6)_B$, J = 14.0 Hz, J = 8.0 Hz, J = 6.0 Hz); 1.91 (d, $H(5)_A$, J = 18.0 Hz); 2.02 (m,

$H(8_A)$); 2.07 (m, $H(8)_B$); 2.21 (dd, $H(5)_B$, J = 18.0 Hz, J = 2.5 Hz); 2.45 (dm, $H(13)_A$, J = 16.0 Hz); 2.68 (dt, $H(13)_B$, J = 16.0 Hz, J = 3.0 Hz). ^{13}C NMR, δ: 15.50 (t, C(3)); 19.36 (q, C(17)); 19.44 (q, C(16)); 19.70 (t, C(8)); 19.88 (q, C(19)); 20.16 (q, C(20)); 22.09 (t, C(11)); 26.66 (d, C(10)); 26.96 (s, C(4)); 27.40 (s, C(12)); 27.92 (d, C(2)); 29.59 (t, C(7)); 32.72 (d, C(15)); 33.37 (d, C(18)); 35.57 (t, C(5)); 38.24 (t, C(13)); 84.77 (s, C(1)); 110.22 (s, C(9)); 150.13 (s, C(14)); 210.52 (s, C(6)).

X-ray diffraction study was carried out on a Bruker P4 diffractometer (Mo-Kα radiation, graphite monochromator, 2θ/θ scan technique in the range of 2θ < 50°). The X-ray data were collected from a single crystal of compound **3** with dimensions 0.80×0.40×0.34 mm. The crystals are orthorhombic: a = 6.0677(8), b = 10.3208(8), c = 28.943(2) Å, V = 1812.5(3) Å^3, space group $P2_12_12_1$, Z = 4, $C_{20}H_{28}O_2$, d_{calc} = 1.101 g cm^{-3}, μ = 0.069 mm^{-1}. The intensities of 1873 independent reflections were measured. The absorption correction was applied taking into account the crystal habitus (transmission was 0.97—0.98). The structure was solved by direct methods using the SHELXS-97 program package. The structure was refined anisotropically by the full-matrix least-squares method (coordinates of the H atoms were not refined) using the SHELXL-97 program package. The parameters of the H atoms were calculated from the coordinates of the corresponding C atoms in each cycle of the refinement. The final refinement based on all F^2 converged to wR_2 = 0.1328, S = 1.068; 200 parameters were refined (R = 0.0498 for 1546 reflections with $F > 4\sigma$). The coordinates and equivalent thermal parameters of the nonhydrogen atoms of molecule **3** were deposited with the Cambridge Structural Database.

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